Unit 2: Adult Stem Cells, and Homeostasis, and Regenerative Medicine

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California State Standards

Biology/Life Science
1.a. Students know cells are enclosed within semipermeable membranes that regulate their interaction with their surroundings.

4.d. Students know specialization of cells in multicellular organisms is usually due to different patterns of gene expression rather than to differences of the genes themselves.

9. As a result of the coordinated structures and functions of organ systems, the internal environment of the human body remains relatively stable (homeostatic) despite changes in the outside environment.

Investigation and Experimentation
1.k. Recognize the cumulative nature of scientific evidence.

1.m. Investigate a science-based societal issue by researching the literature, analyzing data, and communicating the findings.

Goals

Understand the difference between adult and embryonic stem cells.

Understand the diversity of adult stem cells and their functions in the body.

Understand how adult stem cells assist in homeostatic regulation in the body.

Understand how current research of adult stem cells translates to drug development and cell-based therapies.

Objectives

1. The student will be able to demonstrate adult stem cells' role in regeneration in other animal species.
2. The student will be able to demonstrate where adult stem cells are located in the body and realize that we may discover more types of stem cells in the future.
3. The student will be able to describe homeostasis.

4. The student will be able to explain the role of adult stem cells in homeostatic maintenance of the body.
5. The student will be able to differentiate between embryonic stem cells, adult stem cells, and progenitor cells.
6. The student will be able to research how adult stem cells are currently being used to treat disease and which are in clinical trials.
7. The student will be able to identify the steps of a clinical trial and why this process is relevant to regenerative medicine.
8. The student will be able to distinguish between clinical-trial proven therapies and those offered without scientific evidence.

Background Information

Adult stem cells' role in tissue homeostasis

An adult stem cell is an **undifferentiated** cell found in tissues and organs that can **self-renew** and **differentiate** to become most or all of the **specialized** cell types within their specific tissue lineage. Adult stem cells, or **multipotent** cells, have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. They reside in a specific area of each tissue called the "stem cell niche" (The Adult Stem Cell, 2009). The stem cell niche is the **microenvironment** in which the stem cells live, and interacts with stem cells to regulate **cell fate**. Several factors are important in the regulation of stem cell characteristics within the niche, including interactions between stem cells and neighboring cells, **adhesion molecules**, extracellular matrix (ECM) fibers, and signaling molecules such as hormones and proteins (Stem Cell Niche, 2009). (For more information on the microenvironment, see Unit 3, downloadable from http://www.cirm.ca.gov/curriculum_unit-3.)

Every major organ except the pancreas[1] contains resident stem cells that are activated to divide and differentiate into new mature cells of that organ. A major part of organ and tissue homeostasis is the constant or periodic generation of new cells to replace old, damaged, and dying cells. Thus, adult stem cells are the crucial effectors of the regeneration that underlies homeostasis. Adult stem cells normally remain quiescent (non-dividing) for relatively long periods of time until they are activated by signals to maintain tissues, from disease, or from injury. Thus, they are important in maintaining homeostasis in the human body, multicellular animals, and plants. In plants, stem cells in the meristem give rise to new roots, shoots, and flowers. In animals, muscle contains stem cells that contribute to the formation of new muscle after exercise and injury. Red blood cells live for about 120 days, so **hematopoietic stem cells** in bone marrow continuously replace dying red blood cells (Kadereit, 2005) Two specific areas of the brain contain neural stem cells that contribute to the formation of new neurons and supporting **glial cells** throughout life and, evidence suggests, also after traumatic brain injury. Without the action of adult stem cells, you could not heal or achieve cellular- and tissue-level homeostasis.

[1] True stem cells have not yet been identified in the pancreas.

Wound healing

Adult stem cells are also important in the process of wound healing, for example, upon a cut to the skin. Immediately, a set of complex biochemical events takes place in a carefully orchestrated cascade to repair the damage. Wound healing occurs in a four phases: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) remodeling. Within minutes post-injury, hemostasis begins. Platelets (thrombocytes) aggregate at the injury site to form a fibrin clot. This clot acts to control active bleeding, maintaining hemostasis. During the inflammation phase, neutrophils and macrophages degrade bacteria and debris, and damaged cells release factors that cause the migration and division of cells (**progenitor cells**, created by adult stem cells, which have important differences described below) involved in the next, proliferative phase. The proliferation phase is characterized by angiogenesis (capillary growth), collagen deposition, **granulation tissue** formation, **epithelialization**, and wound contraction. In angiogenesis, new blood vessels are formed by vascular endothelial cells. In **fibroplasia** and granulation tissue formation, fibroblasts grow and form a new, provisional ECM by excreting collagen and fibronectin. Concurrently, re-epithelialization of the skin occurs, in which epithelial cells proliferate and “crawl” atop the wound bed, providing cover for the new tissue. During contraction, the wound is made smaller by the action of myofibroblasts, which establish a grip on the wound edges and contract using a mechanism similar to that in smooth muscle cells. In the remodeling phase, collagen is realigned along tension lines and cells that are no longer needed are removed by **apoptosis** (Wound Healing, 2009).

Limb regeneration

Wound healing relies less on stem cell division and differentiation than regeneration. An organism is said to regenerate a lost or damaged part if it regrows so that the original shape and function are restored. Regenerative capacity is inversely related to complexity: in general, a more complex animal part is less capable of regeneration. Whereas newts can regenerate severed limbs, mammals cannot. After a newt limb is amputated, the epidermis migrates to cover the stump in less than 12 hours, forming a structure called the apical epidermal cap. Over the next several days there are changes in the underlying stump tissues that result in the formation of a **blastema** (a mass of undifferentiated adult stem cells). As the blastema forms, pattern formation genes—such as HoxA and HoxD—are activated as they were when the limb was formed in the embryo. The distal tip of the limb (the autopod, which is the hand or foot) is formed first in the blastema. The intermediate portions of the pattern (the arm or leg) are filled in

during growth of the blastema by the process of **intercalation**. Motor neurons, muscle, and blood vessels grow with the regenerating limb, and reestablish the connections present prior to amputation. The length of this process varies according to the age of the animal, ranging from one to three months when the limb becomes fully functional. In mammals, there is limited regeneration in the liver, kidney, ribs, and finger tips. However, there is a genetically-engineered mouse strain, called MRL mice, which exhibits remarkable regenerative abilities for a mammal: they can completely heal ear punctures, spinal cord injuries, and minor heart injuries (Regeneration Biology, 2009).

Characteristics of Adult Stem Cells versus Embryonic Stem Cells

Adult stem cells exist in a very small amount in each tissue type, but have the ability to create the majority of the cell types in that tissue. They do this by differentiating. Differentiation is the process by which a less specialized cell becomes a more specialized cell type. A differentiating cell dramatically changes size, shape, membrane potential, metabolic activity, and responsiveness to signals (Cellular Differentiation, 2009). When an adult stem cell divides, it creates a copy of itself *and* a slightly more differentiated cell. This cell is called a progenitor cell. Progenitor cells usually are the direct precursors of the fully differentiated cell type (there are exceptions, such as in the blood system and the brain, where progenitor cells give rise to more specialized types of precursor cells, which eventually fully differentiate). In other words, a progenitor cell has little plasticity and will only become the cells along a certain lineage (Adult stem cells, 2009). Before we continue, let's review the concept of plasticity.

A cell that can differentiate into all types of body cells is known as **pluripotent**. Embryonic stem cells are pluripotent because they can become any cell in the developing embryo (excluding the placenta; cells that can become any tissue in the body *and* the placenta are called **totipotent**.) Adult stem cells can turn into multiple cell types along a specific lineage; they are multipotent.

Embryonic stem cells and adult stem cells have key differences including location, prevalence within tissues, plasticity/potency, and ultimate lifespan in culture. Embryonic stem cells are only located in the inner cell mass of the blastocyst, which exists 5-14 days after fertilization in humans. Embryonic stem cells are easily isolated from the inner cell mass and can be grown in culture under certain conditions. Multipotent stem cells exist in small quantities in the tissue of the post-blastocyst embryo and onward and are very difficult to isolate. There are very few sources of easily extractable multipotent cells in the adult human body (one relatively easy source is the bone marrow) and those

that are isolated have limited **plasticity** in comparison to embryonic stem cells. Plasticity/potency in relation to stem cells refers to the differential property of stem cell types to alter their differentiation paths. Because of its limited plasticity as compared to a pluripotent embryonic stem cell, a multipotent *adult neural* stem cell, for example, could not eventually create a blood cell (like an embryonic stem cell could). However, recent studies suggest increased plasticity in certain types of adult stem cells, namely hematopoietic (blood) stem cells, which give rise to all types of mature blood cells. In comparison, embryonic stem cells are extremely plastic; they can turn into any cell type. In culture, embryonic stem cells have the ability to grow and divide indefinitely (as long as they are supplied with nutrient medium). Adult stem cells, however, are generally limited to around 30 divisions in culture before they become **senescent** (The Adult Stem Cell, 2009).

Developmental origins of adult stem cells

Gastrulation of the 14-day old embryo leads to three early germ layers: the **endoderm, mesoderm,** and **ectoderm**. At this stage, pluripotent embryonic stem cells begin migrating to these three areas and differentiating. These stem cells give rise to tissues specific to their germ layer. Later, reserves of stem cells that retain the abilities to self-renew and differentiate are used in tissue homeostasis.

Endoderm
The endoderm is the innermost layer of embryonic tissue that is the precursor of the gut, digestive organs, and lungs.

Mesoderm
The mesoderm is embryonic tissue that is the precursor to muscle, connective tissue, bone, kidneys, and other internal organs.

Ectoderm
The ectoderm is the outermost layer of embryonic tissue that is the precursor of the epidermis (skin), nervous system, and sensory organs.

Adult stem cell types

The best-characterized types of adult stem cells include hematopoietic stem cells, mesenchymal stem cells, neural stem cells, and epithelial stem cells.

Hematopoietic stem cells give rise to all the blood cell types including the **myeloid** lineage (monocytes and macrophages, neutrophils, basophils, eosinophils,

megakaryocytes/platelets, dendritic cells), the **lymphoid** lineage (T-cells, B-cells, NK-cells), the **erythroid** lineage (erythrocytes, a.k.a. red blood cells), and possibly the cells that make bone (osteoblasts). They are found in the bone marrow from very early on in development, as well as in umbilical cord blood and placental tissue (Hematopoietic stem cell, 2009).

Mesenchymal stem cells can differentiate into cartilage cells **(chondrocytes)**; muscle cells **(myocytes)**; fat cells **(adipocytes)**; tendons, ligaments, and connective tissue (including **osteoblasts**). Mesenchymal stem cells are located throughout the body and for this reason are difficult to isolate. A progenitor of the mesenchymal stem cell is a muscle stem cell. The muscle stem cell resides as a satellite cell in the muscle tissue. Satellite cells are small mononuclear progenitor cells with virtually no cytoplasm. Quiescently, they are found sandwiched between the basement membrane and sarcolemma (cell membrane) of individual muscle fibers. When an injury occurs to the muscle, the satellite cells are activated to proliferate and migrate to the damaged area. Once there, they begin differentiating into myoblasts, which then develop into single fibers which will fuse together to form a mature muscle fiber (Mesenchymal stem cell, 2009).

Neural stem cells in adult mammals are located in the *subventricular zone* lining the lateral ventricles, where they give rise to newly-born neurons that migrate to the olfactory bulb via the rostral migratory stream, as well as the *subgranular zone* which is part of the dentate gyrus of the hippocampus. These regions are responsible for, among other things, smell and memory (respectively). Neural stem cells (also called neural precursor cells) directly give rise to progenitors of **neurons**, **oligodendrocytes**, and **astrocytes** through the process of **neurogenesis**. Newly-born neurons reach the olfactory bulb and mature into neurons that have specific chemical receptors that allow the detection and discrimination of a multitude of smells. These neurons are frequently damaged because of direct exposure to air and can be regenerated. Neurogenesis in the hippocampus is negatively affected by stressful experiences, while exercise and learning increase the number of new neurons in these areas (Neurogenesis, 2009).

Epithelial stem cells give rise to **epithelial cells** which constitute 60 percent of the differentiated cells in the body (The Adult Stem Cell, 2009). They are responsible for covering the internal and external surfaces of the body, including the lining of vessels, glands, and other cavities. The epithelial cells in skin and the digestive tract are replaced constantly. Other epithelial cell populations—in the ducts of the liver or pancreas, for example—turn over more slowly. The cell population that renews the

epithelium of the small intestine occurs in the intestinal crypts, deep **invaginations** in the lining of the gut. The **crypt cells** are often regarded as stem cells. Epithelial stem cells of the skin are called **epidermal stem cells**. They are found in the bulge region of the outer root sheath of the hair follicle, the interfollicular epidermis, and the sebaceous gland. Further investigation showed that cells in the bulge region of the hair follicle are more primitive—giving rise to multiple skin cell types. Epidermal stem cells undergo asymmetric cell division, where one daughter cell remains a stem cell and the other will differentiate into a transient amplifying cell that will divide several more times and generate larger quantities of specialized differentiated cells within the epidermis. For more information on epidermal stem cells see http://njms.umdnj.edu/gsbs/stemcell/scofthemonth/EpSClay.htm.

Adult stem cell therapies

Adult stem cells are used in therapy. The most well known adult stem cell therapy is a bone marrow transplant. Since its first successful use in 1968, bone marrow transplants have been used to treat patients diagnosed with **leukemia**, **aplastic anemia**, **lymphomas** such as **Hodgkin's disease**, **multiple myeloma**, **immune deficiency disorders** and some solid tumors such as breast and ovarian cancer. Importantly, a bone marrow transplant does not have a 100% cure rate, although it has saved many lives. Thus it usually represents a treatment, not an absolute cure, for these diseases.

There are three kinds of bone marrow transplants:

- Autologous bone marrow transplant. *Auto* means *self*. Stem cells are taken from the patient before the patient gets chemotherapy or radiation treatment. When chemotherapy or radiation is done, the patient gets their stem cells back. This is called a "rescue" transplant.
- Allogeneic bone marrow transplant. *Allo* means *other.* Stem cells come from another person, who is called a donor. Donor stem cells come from the donor's bone marrow or their blood. Most times, a donor must have the same **genetic typing** as the patient, so that their blood and tissue types "match" the patient's. Special blood tests will tell whether a possible donor is a good match for the patient. A patient's brothers and sisters have the highest chance of being a good match. Sometimes, parents and children of the patient and other relatives may be matches. Donors who are not related to the patient may be found through national bone marrow registries—lists of people who have offered to be donors

(Johnson, 2008). In the United States, there is a dire shortage of bone marrow and organ donors from people of mixed race. This decreases the likelihood of finding a good match for people needing bone marrow transplants from minority groups.

- Umbilical cord blood transplant. Stem cells are taken from an umbilical cord right after delivery of an infant. Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system. Also, because umbilical cord blood lacks well-developed immune cells, there is less chance that the transplanted cells will attack the recipient's body, a problem called graft versus host disease. The stem cells are tested, typed, counted, and frozen until they are needed for a transplant. This could be years later, if stored properly in a cord blood bank.

Most patients get high doses of chemotherapy, radiation, or both, before the bone marrow transplant. This is called **ablative** (or **myeloablative**) treatment. It kills any cancer cells that might remain, and it makes room in the bone marrow for the new stem cells to grow. Some patients receive less chemotherapy and radiation before their transplant. This is called a reduced intensity (non-myeloablative) or "mini" transplant. After the patient gets chemotherapy and radiation, a doctor will do the stem cell transplant. The patient gets the stem cells through a tube called a central venous catheter. The cells go right into the bloodstream. This delivery of cells is called an infusion. It may take up to several hours. It is not surgery; it is similar to a blood transfusion. The stem cells find their way into the bone marrow, where they may begin reproducing and making healthy new blood cells (Chen, 2008).

Adult stem cells have also been used to create a tissue specific organ. In November 2008, scientists in Spain carried out a trachea transplant for a woman whose windpipe had been damaged by tuberculosis. The doctors took adult stem cells and some other cells from the healthy right airway of the woman needing the trachea transplant, grafted those cells onto the stripped-down donated (cadaver) trachea, and marinated the trachea in chemicals in a lab to coax the trachea into rebuilding itself. When the trachea was ready, the doctors implanted it into the patient. The procedure worked—and since the trachea had been prepped by the patient's own stem cells before transplantation, her body accepted it without immune-suppressing drugs. Usually these are delivered along with **allogeneic** bone marrow transplants to decrease the likelihood of rejection

and graft versus host disease, although often the patient is susceptible to opportunistic infections. (Hitti, 2008)

U.S. adult stem cell clinical trials

There also many adult stem cell therapies in clinical trial. If one searches on the NIH website for clinical trials, http://www.clinicaltrials.gov, there are over 2,000 trials involving adult stem cells. The clinical trial process is long and complicated. Clinical trials and research are studies done to answer specific questions about novel vaccines and therapies, as well as new ways of using known treatments. The entire Food and Drug Administration (FDA) approval process can take up to nine years, depending on many factors.

Clinical trials are conducted in four phases. The trials at each phase have a different purpose and help answer different questions. In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely. In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use (Understanding Clinical Trials, 2007).

All clinical trials must be conducted according to strict scientific and ethical principles. Every clinical trial must have a protocol, or action plan that describes what will be done in the study, how it will be conducted, and why each part of the study is necessary. This includes details such as the criteria for patient participation, the schedule of tests, procedures, and medications, and the length of the study. As a clinical trial progresses, researchers report the results of the trial at scientific meetings and in medical journals as well as to various government agencies (What is a Protocol?, 2008).

Patient participation in a clinical trial is voluntary. Before joining a trial a patient will receive an informed consent document that includes details about the study, such as its purpose, duration, and required procedures. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign

the document and comply with the conditions. However, informed consent is not a binding contract, and the participant may withdraw from the trial at any time (Understanding Clinical Trials, 2007).

The ISSCR has released *Guidelines for the Clinical Translation of Stem Cells* that examine the scientific, clinical, regulatory, ethical and societal issues that must be addressed to ensure that basic stem cell research is responsibly transitioned into appropriate clinical applications. The guidelines present 40 recommendations to ensure the safety of patients, the ethical nature of the trials, and validity of the clinical results (Guidelines for the Clinical Translation of Stem Cells, 2008). You can find all the guidelines at http://www.isscr.org/clinical_trans/index.cfm.

Here are a few of these recommendations:

"Recommendation 3: In the case of donation for allogeneic use, the donor should give written informed consent that covers, where applicable, the following issues:

a) Cells and/or cell lines may be subject to storage. If possible, duration of storage should be specified;

b) The donor may (or may not) be approached in the future to seek additional consent for new uses, or to request additional material (blood or other clinical samples) or information;

c) The donor will be screened for infectious and possibly genetic diseases;

d) The donated cells may be subject to genetic modification by the investigator;

e) With the exception of directed altruistic donation, the donation is made without restrictions regarding the choice of the recipient of the transplanted cells;

f) Disclosure of medical and other relevant information that will be retained, and the specific steps that will be taken to protect donor privacy and confidentiality of retained information, including the date at which donor information will be destroyed, if applicable;

g) Explanation of what types of genomic analyses (if any) will be performed and how genomic information will be handled; and

h) Disclosure that any resulting cells, lines or other stem cell-derived products may have commercial potential, and whether any commercial and intellectual property rights will reside with the institution conducting the research."

"Recommendation 20: Stem cell-based clinical researchers should:

a) Cooperate with and share scientific expertise to assist other investigators and human subjects research review committees in assessing:

   i. The biological characteristics of the cells to be used in clinical trials;

   ii. Whether these cells have been developed with appropriate manufacturing standards;

   iii. Preclinical data on their use in animal and/or other models for evaluating their safety and efficacy; and

   iv. Any early clinical data, if available, which address safety issues in the short and medium term and continued observation for long term effects;

b) Address the risks of stem cell-based interventions including, for example, cell proliferation and/or tumor development, exposure to animal source materials, risks associated with viral vectors, and risks as yet unknown;

c) Provide the utmost clarity regarding the potential benefits of participating in the trial with stem cells, since patients may have recourse to reasonable therapeutic alternatives; the informed consent process must emphasize the novel and experimental aspects of cell based interventions. It is important to minimize misconceptions patients may have about the potential for therapeutic efficacy;

d) Disclose any financial and non-financial conflicts of interest among the investigators, sponsors, and institutions in which the stem cell research is being conducted;

e) Monitor research subjects for long-term health effects and protection of the confidentiality of their health data;

f) Provide a clear, timely, and effective plan for adverse event reporting;

g) Offer a clinical plan to provide treatment for toxicity, including treatment of tumors that might arise. This plan might include compensation for research-related injuries; and

h) Ensure that insurance coverage or other appropriate financial or medical resources are available to patients to cover potential complications arising from their research participation."

Stem Cell Tourism

There is only one phase 1 embryonic stem cell therapy, for spinal cord injury, in Food and Drug Administration clinical trials. It is important to know that drugs including stem cells in the clinical trial process are only available to participants in the trials, and they usually must stop all other treatments before beginning the trial. Those who wish to obtain the drug, yet are either not qualified for a clinical trial or are perhaps qualified but given a placebo, often take desperate measure to obtain these therapies. In what is called "stem cell tourism" patients travel to other countries with less restrictions to receive stem cell therapies. These therapies are sometimes experimental and can be dangerous, although there are many legitimate therapies going through the national regulatory processes in these countries. The number of patients who have traveled abroad for stem cell therapies is unknown, though experts say that anecdotally it appears to be thousands. The proliferation of clinics marketing purportedly effective stem cell interventions online has many experts worried. A December 2008 study of stem cell clinic web sites found that they claimed to treat a range of diseases that go beyond the scope of the early evidence on stem cells' efficacy, while playing up the benefits and talking little about risks. The study, published in the journal *Cell Stem Cell*, found that the average price tag for a stem cell treatment abroad, excluding travel and lodging costs, was $21,500 (O'Reilly, 2009). Recently, China and European countries have begun to crack down on stem cell tourism, releasing ethical guidelines aimed at discouraging doctors from offering patients unproven or sham (fake) treatments based on stem cells (Coghlan, 2009).

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Links

http://www.cirm.ca.gov/curriculum_unit-2 (Supplementary Adult Stem Cell PowerPoint and Appendix Materials)

http://www.cirm.ca.gov/curriculum_unit-3 (Materials on the microenvironment)

http://stemcells.nih.gov/info/basics/basics4.asp

http://www.isscr.org/public/adultstemcells.htm

http://www.nlm.nih.gov/medlineplus/ency/article/003009.htm

http://cpmcnet.columbia.edu/dept/medicine/bonemarrow/bmtinfo.html

http://learn.genetics.utah.edu/content/tech/stemcells/sctoday/

http://www.webmd.com/news/20081119/1st-trachea-transplant-from-stem-cells

http://clinicaltrials.gov/ct2/info/understand

http://www.nlm.nih.gov/services/ctprotocol.html

http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf

http://www.ama-assn.org/amednews/2009/02/02/prsb0202.htm

http://www.newscientist.com/article/dn17725-china-cracks-down-on-stem-cell-tourism.html

Marrow donors are rare for mixed-race patients: http://www.cbsnews.com/stories/2009/05/27/health/main5044251.shtml?source=RSSattr=Health_5044251

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http://en.wikipedia.org/wiki/Wound_healing

http://en.wikipedia.org/wiki/Regeneration_(biology)

http://en.wikipedia.org/wiki/Adult_stem_cell

http://en.wikipedia.org/wiki/Transdifferentiation

http://en.wikipedia.org/wiki/Hematopoetic_stem_cells

http://en.wikipedia.org/wiki/Satellite_cell

Glossary

Ablative (myeloablative) - agents that destroy bone marrow activity. They are used to prepare patients for bone marrow or stem cell transplantation.

Adipocytes (fat cells) - a connective tissue cell that has differentiated and become specialized in the synthesis (manufacture) and storage of fat.

Allogeneic - taken from different individuals of the same species. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical.

Aplastic anemia - a condition where bone marrow does not produce sufficient new cells to replenish blood cells.

Apoptosis - the process of programmed cell death that may occur in multicellular organisms

Astrocytes - are characteristic star-shaped glial cells in the brain and spinal cord. They perform many functions, including biochemical support of endothelial cells which form the blood-brain barrier, provision of nutrients to the nervous tissue, maintenance of extracellular ion balance, and a principal role in the repair and scarring process of the brain and spinal cord following traumatic injuries.

Beta-pancreatic islet cells - are a type of cell in the pancreas in areas called the islets of Langerhans. Beta cells make and release insulin, a hormone that controls the level of glucose in the blood.

Blastema - a mass of undifferentiated adult stem cells that in newts gives rise to a new limb.

Cell fate - The ultimate differentiated state to which a cell has become committed.

Chondrocytes (cartilage cells) **-** They produce and maintain the cartilaginous matrix, which consists mainly of collagen and proteoglycans.

Crypt cell - Crypt cells reside in the intestinal crypts and are sites of digestion and nutrient absorption. They have hair-like protrusions called microvilli that aid in these processes. Intestinal crypt stem cells are responsible for the turnover of intestine cells.

Differentiate - the process by which a less specialized cell becomes a more specialized cell type

Ectoderm - The outermost of the three primary germ layers of an embryo, from which the epidermis, nervous tissue, and, in vertebrates, sense organs develop

Endoderm - the innermost of the three germ layers. The endoderm gives rise to the epithelium of the pharynx, including the eustachian tube, the tonsils, the thyroid gland, parathyroid glands, and thymus gland; the larynx, trachea, and lungs; the gastrointestinal tract (except mouth and anus), the urinary bladder, the vagina, and the urethra.

Epidermal stem cell - this stem cell replenishes skin, hair follicles, and sebaceous glands through the processes of asymmetric cell division and transient amplification.

Epithelialization - the regrowth of skin over a wound.

Epithelial cells (tendons, ligaments, and connective tissue, includes osteoblasts) - Epithelial cells line the inside surfaces of fluid or air-filled tubes and spaces within the body. Epithelium may be protective (as in the skin) or secretory (as in the cells lining the wall of the gut).

Erythroid - describes a lineage of cells that gives rise to erythrocytes, or red blood cells

Fibroplasia - the formation of a scar during the fibroblastic repair phase of healing.

Genetic typing - refers to the process of determining the genotype of an individual by the use of biological assays.

Glial cells - non-neuronal cells that provide support and nutrition, maintain homeostasis, form myelin, and participate in signal transmission in the nervous system.

Granulation tissue - fibrous connective tissue that replaces a fibrin clot in healing wounds. Granulation tissue typically grows from the base of a wound and fills wounds of almost any size.

Hematopoietic stem cells - multipotent stem cells that give rise to all the blood cell types including myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells).

Homeostasis - the ability to regulate internal conditions, usually by a system of feedback controls, so as to stabilize health and functioning amidst outside changing conditions.

Immune deficiency disorders - condition where the body's defense system is compromised, causing it to be less resilient to foreign invading cells.

Intercalation - the reversible inclusion of a molecule between two other molecules

Invagination - Invagination is the morphogenetic processes by which an embryo takes form, and is the initial step of gastrulation, the massive reorganization of the embryo from a simple spherical ball of cells, the blastula, into a multi-layered organism, with differentiated germ layers: endoderm, mesoderm, and ectoderm. More localized invaginations also occur later in embryonic development, to form coelom, etc.

Leukemia - is a cancer of the blood or bone marrow and is characterized by an abnormal proliferation (production by multiplication) of blood cells, usually white blood cells (leukocytes)

Lymphomas (**Hodgkin's disease) -** is a cancer that begins in the lymphocytes of the immune system and presents as a solid tumor of lymphoid cells

Mesoderm - The middle layer of the three primary germ cell layers. It differentiates to gives rise to a number of tissues and structures including bone, muscle, connective tissue, and the middle layer of the skin

Microenvironment - a specific set of physical, biological, and chemical factors immediately surrounding the cell

Multipotent - stem cells can differentiate into a number of cells, but only those of a closely related family of cells.

Multiple myeloma - a cancer of the white blood cells known as plasma cells. A type of B cell, plasma cells are a crucial part of the immune system responsible for the production of antibodies in humans

Myeloid - Referring to the non-lymphocytic groups of white blood cells, including the granulocytes, monocytes and platelets.

Myocytes (muscle cells) - the type of cell found in muscles. There are various specialized forms of myocytes: cardiac, skeletal, and smooth muscle cells, with various properties.

Neurogenesis - is the process by which neurons are generated. Neurogenesis does indeed continue into and throughout adult life with examples of neurogenesis found in the hippocampus of mammals, and the olfactory bulb.

Neurons - an excitable cell in the nervous system that processes and transmits information by electrochemical signaling. Neurons are the core components of the brain, the vertebrate spinal cord, the invertebrate ventral nerve cord, and the peripheral nerves.

Oligodendrocytes - are a type of brain cell. Their main function is the insulation of axons (the long projection of nerve cells) in the central nervous system (the brain and spinal cord) of higher vertebrates.

Osteoblasts - a mononucleated cell that is responsible for bone formation.

Phagocytized (phagocytosis) - the process by which certain cells engulf and destroy microorganisms and cellular debris

Pluripotent - the ability of the human embryonic stem cell to differentiate or become almost any cell in the body

Progenitor cells - is an early descendant of a stem cell that can only differentiate, but it cannot renew itself anymore. It is limited to differentiate on a specific cell lineage.

Self-renew - the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

Senescent - the biological changes which take place in cell as it ages, which includes the halting of cell division

Specialized - Specialized cells perform specialized functions in multicellular organisms. Groups of specialized cells cooperate to form a tissue, such as a muscle.

Totipotent - the ability of a single cell to divide and produce all the differentiated cells in an organism, including extraembryonic tissues

Undifferentiated - Of, or describing a cell that has not yet acquired a special structure and function; pertaining to an immature cell or a primitive cell

Outline of Unit

I. Invitation
   A. What do sea star arms (star fish), lizard tails, and your liver have in common?
      i. Prometheus (bird eating liver everyday – then regrowing!?)
         1. Why would the liver need to regenerate?
         2. Do you think this will ever be possible for humans or animals?
      ii. Article with graphics about the myth: http://www.thanasis.com/modern/pro01.htm
      iii. Did ancient Greeks know about liver regeneration? Free pdf of article (AP extension or teacher background) http://www.annals.org/cgi/content/abstract/149/6/421

SYNOPSIS of the Myth of Promethius: Epimetheus and Prometheus, Titans, aid Zeus in a war against Atlas and the rest of the Titans. Zeus wins and grants the two Titans the ability to create creatures to populate Earth. Epimetheus gives all the best qualities, like strength and flight, to animals—leaving no good attribute for men. Prometheus gives men the ability to walk upright, and to look towards Olympus. He also gives men fire, but tricks Zeus into accepting the inedible parts of animal sacrifices. Zeus, angered at Prometheus, takes fire away from Man! But Prometheus steals it back. Zeus punishes Prometheus by chaining him onto the Andes Mountains and having an Eagle eat his liver every day. However, Promethius' liver grows back every night. Zeus finally takes pity and allows Chiron (an Immortal Centaur in excruciating pain from Heracles' poison arrow) to sacrifice himself for Prometheus' freedom. Heracles kills the eagle, and everyone is happy.

   B. What cells in your body are responsible for regeneration?
      i. Where are they? Have students fill out a black line master to indicate where we might have "regenerative" cells. (Or print as transparency and write answers with dry-erase)
         1. Anatomically correct black-line masters of man and woman. http://upload.wikimedia.org/wikipedia/commons/f/f5/Human_body_features.svg
         2. Discuss as a class
            a. For more beginning students, it is safe to say that there are "regenerative" cells EVERYWHERE in the body except the pancreas. Mention the major adult stem cell types: hematopoietic, mesenchymal, and neural.

   b. For more advanced students, you can discuss hematopoietic, mesenchymal, neural, endothelial, and epithelial stem cells and locations from the background information section or the supplementary PowerPoint provided with unit 2 AND the function of progenitor cells.
3. Any putative stem cell populations? Where haven't we found stem cells? Do all stem cells participate in regeneration?
   a. Horizontal basal cells in the Olfactory bulb: abstract and full text from http://www3.interscience.wiley.com/journal/121587503/abstract?CRETRY=1&SRETRY=0
      i. Which type of olfactory bulb cell is the stem cell is controversial, and the role in regeneration is still being characterized
      ii. Students can read summary of paper provided at http://cirm.ca.gov/curriculum_unit-2
   b. Kidney SCs: Abstract and whole text from http://content.karger.com/ProdukteDB/produkte.asp?doi=10.1159/000117311
      i. Presence of stem cells controversial and function unknown.
   c. Retinal SCs: Two news articles
      i. http://www.foxnews.com/story/0,2933,228203,00.html
         1. Claims retina has stem cells
      ii. http://www.sciencedaily.com/releases/2009/03/090330200833.htm
         1. Claims these cells were misidentified.
4. **AP extension:** how do scientists identify stem cells? What are the characteristics of a stem cell? Use above papers and this paragraph from Wikipedia: Stem Cell

Identification

The practical definition of a stem cell is the functional definition - a cell that has the potential to regenerate tissue over a lifetime. For example, the gold standard test for a bone marrow or hematopoietic stem cell (HSC) is the ability to transplant one cell and save an individual without HSCs. In this case, a stem cell must be able to produce new blood cells and immune cells over a long term, demonstrating potency. It should also be possible to isolate stem cells from the transplanted individual, which can themselves be

transplanted into another individual without HSCs, demonstrating that the stem cell was able to self-renew.

Properties of stem cells can be illustrated *in vitro*, using methods such as clonogenic assays, where single cells are characterized by their ability to differentiate and self-renew. As well, stem cells can be isolated based on a distinctive set of cell surface markers. However, *in vitro* culture conditions can alter the behavior of cells, making it unclear whether the cells will behave in a similar manner *in vivo*. Considerable debate exists whether some proposed adult cell populations are truly stem cells.

C. Discuss similarities and differences between wound healing and regeneration
   i. http://www.hhmi.org/biointeractive/stemcells/lectures.html
   ii. View Lecture 2, Adult Stem Cells and Regeneration
   iii. Use HHMI video adult stem cells handout (student version) for students to answer as they watch the lecture. See teacher version for answer key. (Download both from Appendix A, http://www.cirm.ca.gov/curriculum_unit-2)

SYNOPSIS: Wound healing uses blood clotting factors (CF's) and hormone/protein signals, like Thrombin, to recruit layers of platelet cells which clog the wound, allowing the dermis/capillary to regrow over the wound. This regrowth can use stem cells, but isn't largely due to stem cell division. [Note: Adult stem cells support the constant generation of new cells to replace old, damaged, and dying cells. They also participate in injury repair; for example, when muscle is injected with snake venom, muscle satellite cells (stem cells) divide, migrate to the injury site, differentiate, and fuse together to form new muscle fibers.] Regeneration can occur due to a limb being severed (as with the newt) or from chemical degradation (as in the liver). In limb regeneration, the wound first heals, then a blastema (group of cells) forms, inside which are differentiating stem cells. In this way, stem cells begin to reform the regenerating body part. Thus, regeneration—rather than wound healing—relies much more heavily on stem cell division and differentiation, coupled with molecules which signal regeneration to occur.

II. Exploration
    A. What are some different types of Adult vs. embryonic stem cells? (EASY) Interactive animation from – Learn Genetics (University of Utah) http://learn.genetics.utah.edu/content/tech/stemcells/sctypes/
    Note: Fetal stem cells are *not* typically considered Pluripotent or equivalent to embryonic stem cells. Please clarify this with your students.
        i. While doing the interactive animation, have students fill out "Stem Cells: What are they? A Great Overview!" handout Download at http://stemcellcontroversy.weebly.com/-background-information.html by clicking the Download file link under stem_cell_basics.doc
        ii. Through this, you will explore:
            1. Plasticity: Totipotent vs. Pluripotent vs. Multipotent
            2. Plasticity's underlying process: Differentiation
                a. What drives differentiation? – through gene regulation (See microenvironment unit)
                b. AP extension topics (GOOGLE)
                    i. Things that regulate differentiation:
                        1. Extracellular signals
                        2. Transcription factors and miRNAs (**ADVANCED**)
                        3. Epigenetics
        iii. As they are, adult stem cells are able to produce one or several types of mature cells rather than many types of cells for mature tissues (embryonic stem cells) or all types of cells (totipotent cells from the morula).
            1. Ex. Muscle stem cell cannot create blood, whereas embryonic stem cells can become anything up to a certain time point in their development
            2. Difference between stem cells and progenitor cells
                a. Think of adult stem and progenitor cells as having different levels of potential, based on how many different types of cells they are able to become or turn into.
                b. In reality there is a continuum of plasticity/potency, and scientists have named and characterized just some of the discrete levels.
                c. A stem cell is generally multipotent, while a progenitor cell is generally unipotent.
    B. Homeostasis

i. What is homeostasis?
    1. Video from how stuff works http://health.howstuffworks.com/adam-200092.htm
    2. Discussion question: How are these types of homeostasis (e.g., the body's thermostat, glucose/insulin hormone negative feedback) different from the maintenance of cells in tissue homeostasis?

ii. Describe adult stem cells' role in human tissue homeostasis

iii. **Planaria regeneration lab**
    1. *Watch video* as lead in. "Planarian Regeneration and Stem Cells" from Potent Biology: Stem Cells, Cloning, and Regeneration, HHMI Holiday lectures 2006. http://www.hhmi.org/biointeractive/stemcells/planarian_regen.html
        a. *Use student questions* that go with the video – "Planarian Regeneration and Stem Cells Video Handout" with teacher version. Downloadable from CIRM education portal (http://www.cirm.ca.gov/curriculum_unit-2) in Appendix B.

SYNOPSIS: Describes the basic biology of *Planaria*. It has the ability to regenerate any part of its body, down to when it's cut into 279 fragments. Neoblasts (totipotent stem cells) migrate to areas of damage and create specific differentiated cells in order to regenerate the damaged parts of its body. RNAi experiments portray 240 genes involved in regeneration. One molecule *smedwe* is found in Drosophilia stem cells (involved in gonad cells of female fruit flies). Without this protein the *Planaria* die because the head begins to curl inward. In the future these experiments may allow use of *planaria* to identify gene function in humans and vertebrates.

2. Discussion questions: Are human adult stem cells equivalent to planaria neoblasts? Do they have the same potential? Answer: No, planaria neoblasts can regenerate the entire organism while adult stem cells in humans are restricted to regenerating tissue-specific lineages.
3. Use the Northwest Association for Biomedical Research intro PowerPoint, lab protocol, and handouts within the Stem Cell Curriculum available for download http://www.nwabr.org/education/stemcell.html → follow the link titled "Click here to submit your information and be directed to the Stem Cell Curriculum page"
4. Use NWABR planaria regeneration protocol.

a. The brown planaria, *Dugesia tigrina,* and black planaria, *Dugesia dorotocephala,* can be purchased from commercial supply houses, such as **WARDS** and **Boreal/Science Kits**.
    i. http://www.wardsci.com
    ii. http://www.sciencekit.com

C. Regenerative medicine: what is it?
    i. Treatment possibilities using adult and embryonic stem cells
        1. Right now, RM is restricted to adult stem cells and drugs associated with them. (Embryonic stem cells have not gotten to the same point in pre-clinical research and clinical trials as certain adult stem cells. There is a pending clinical trial involving Geron's technology which utilizes differentiated embryonic stem cells to treat spinal cord injuries. More information from The Niche blog: http://blogs.nature.com/reports/theniche/2009/08/first_embryonic_stemcell_trial.html)
    ii. Jigsaw activity: What are examples in the natural world of regeneration? How do humans compare? What cells play a role in lizard tail regeneration? What is the goal of regenerative research and medicine?
        1. MID level overview http://www.sci-ctr.edu.sg/ssc/detailed.jsp?artid=5451&type=6&root=4&parent=4&cat=45
        2. CHALLENGING overview http://discovermagazine.com/2007/apr/how-to-grow-a-new-limb
        3. Lizard tail and salamander limb regeneration
            a. EASY- about reptiles and tail regeneration http://www.factmonster.com/dk/encyclopedia/reptiles.html#ENCY117REGENE
            b. MID- more about caudal autonomy http://discovermagazine.com/2005/may/ask-discover
            c. CHALLENGING- research on salamander limb regeneration http://www.scientificamerican.com/article.cfm?id=contest-inspires-limb-regeneration
        4. Zebrafish limb regeneration and epigenetic control

a. CHALLENGING- http://www.sciencedaily.com/releases/2009/11/091102171419.htm

5. "Mighty mouse" with enhanced regenerative capacity
   a. MID- Mice that regrow organs http://www.wired.com/medtech/genetics/news/2005/09/68962#
   b. MID- expansion on above and aging http://www.thefreelibrary.com/Rare+regeneration+fixes+pierced+mouse+ears-a020396424
6. Metazoans
   a. MID- Regeneration research quote http://www.wired.com/wiredscience/2007/04/scientists_sear/
7. Research on Human regeneration
   a. MID- How animal research leads to knowledge about human regeneration http://www.wired.com/medtech/genetics/news/2006/09/71817?currentPage=all
8. MID-heart regeneration http://www.reuters.com/article/scienceNews/idUSTRE53166P20090402

D. What are the potential uses of adult stem cells?
   i. Adult stem cell-based therapies (that exist today, also the possibility of growing organs in the future) http://learn.genetics.utah.edu/content/tech/stemcells/sctoday/
   ii. Drugs that affect or target stem cells (breast cancer drug) http://www.medicalnewstoday.com/articles/163760.php
   iii. Using stem cells to test/screen drugs in vitro http://www.hsci.harvard.edu/newsroom/stem-cells-tools
   iv. Diagram of potential uses http://en.wikipedia.org/wiki/File:Stem_cell_treatments.svg

E. Process and importance of clinical trials
   i. Explain steps in clinical trials, preclinical through phase 4. See Background information section and associated web readings and resources (listed below).
   ii. Also use the Student handout: Clinical trials information chart (see teacher version for answers) in Appendix C at cirm.ca.gov/unit-2
   iii. Web resources
      1. MID- overview of adult stem cell clinical trials and some companies involved http://seekingalpha.com/article/143912-adult-stem-cell-drugs-and-therapies-are-the-next-big-market

2. MID- explanation of FDA and clinical trials process http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121345.htm
   OR
   MID-CHALLENGING- explanation of clinical trial design http://clinicaltrials.gov/ct2/info/understand
3. MID- dose response curve http://www.merck.com/mmpe/sec20/ch304/ch304d.html
4. MID-CHALLENGING – difficulties in bringing research to therapies http://www.newsweek.com/id/166856
5. MID – can we use undifferentiated embryonic stem cells for therapies? http://www.cirm.ca.gov/node/2089
6. The Drug Pipeline
   a. Simple pipeline diagram
   b. More complicated FDA pipeline: Nature

III. Application

A. Clinical Trial exercise
   i. Use Regenerative medicine and clinical trials research project handout (Appendix D)
   ii. Students choose diseases from 70+ diseases list (Appendix E)
   iii. Students do Preliminary research using forms (Appendix F): how many hits, general type of therapy (cell-based, drug, etc.) Find any stem cell therapies on the market for these diseases (there may not be an example.)
   iv. Narrow down to one disease. Answer questions on Regenerative medicine and clinical trials research project handout.
   v. Use the information found to create a PowerPoint presentation summarizing the clinical trial results from chosen disease. (See examples of student work: Appendix G, http://www.cirm.ca.gov/curriculum_unit-2)

OR

B. If you were an adult stem cell, what kind would you be?
   i. Write an essay explaining why you are important, where you work, and a detailed description of how you keep the body healthy and in homeostasis.
   ii. Or they can draw all these as a cartoon/storyboard to ultimately be turned into an animation?
   iii. Or create a pamphlet about why you should be a certain type of adult stem cell?

IV. Assessment

A. What are some different types of stem cells?
B. Fill out characteristics of embryonic and adult stem cells vs. progenitor cell table (under Assessment, http://www.cirm.ca.gov/curriculum_unit-2)
C. What is homeostasis and why is it important to living organisms?
D. Where have we found adult stem cells?
E. Why are scientists studying star fish (or planaria) regeneration in relationship to human limbs?
F. Why do we need adult stem cells?
G. What are some of the current uses of adult stem cells?
H. What are the steps in clinical trials and what do they mean?

Additional Resources

Check Medical News Today, Wired.com, New Scientist, ScienceDaily for updates.

Powerpoints/videos about regenerative medicine; includes lesson plans, scientific animations and scientist lecture videos:
http://outreach.mcb.harvard.edu/materials.htm

HHMI Activities that go along with lectures – planaria regeneration lab
http://www.hhmi.org/biointeractive/activities/index.html

Simple pipeline diagram:
http://www.psoriasis.org/netcommunity/researchers_pipeline
More complicated FDA pipeline: Nature
http://www.nature.com/nrd/journal/v5/n6/fig_tab/nrd2033_F1.html

Where are the Cures? Valley of Death.
http://www.newsweek.com/id/166856

Using undifferentiated human Embryonic Stem Cells for therapies? NO!
http://www.cirm.ca.gov/node/2089
FDA clinical trials FAQ:
http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121345.htm

Clinicaltrials.gov:
http://clinicaltrials.gov/ct2/info/understand

From Idea to Market: The Drug Approval Process
http://www.jabfm.org/cgi/reprint/14/5/362.pdf

Dose response curve, Merck:
http://www.merck.com/mmpe/sec20/ch304/ch304d.html

Eye Cells Believed To Be Retinal Stem Cells Are Misidentified
http://www.sciencedaily.com/releases/2009/03/090330200833.htm

Scientists Search Starfish For Key to Human Regeneration
http://www.wired.com/wiredscience/2007/04/scientists_sear/

Mighty Mice Regrow Organs (strain that regenerates better, trying to figure out why.)
http://www.wired.com/medtech/genetics/news/2005/09/68962#

Grow Your Own Limbs
http://www.wired.com/medtech/genetics/news/2006/09/71817?currentPage=all

Info and pictures about lizard tail regeneration – easy
http://www.factmonster.com/dk/encyclopedia/reptiles.html

Info about adult stem cells from NIH
http://stemcells.nih.gov/info/basics/basics5.asp

Animation on homeostasis
http://health.howstuffworks.com/adam-200092.htm

Interactive physiology about homeostasis
http://ats.doit.wisc.edu/biology/ap/ho/ho.htm

Retinal stem cells video
http://videos.howstuffworks.com/hsw/26397-body-and-brain-retinal-stem-cells-video.htm

Regenerating livers/ other related videos at this link as well
http://videos.howstuffworks.com/discovery/29534-assignment-discovery-regenerating-livers-video.htm

Blood cells and stem cells
http://videos.howstuffworks.com/hsw/5953-blood-a-comparison-of-blood-cells-video.htm

Researchers Identify Major Source of Muscle Repair Cells; Implications For Treating Duchenne's Muscular Dystrophy:
http://www.sciencedaily.com/releases/2006/01/060131085949.htm

HHMI Video Adult Stem Cells and Regeneration Part 2 of 6 giving the information about regeneration vs. wound healing. On Youtube this whole series is available in about 10 minute parts.
http://www.youtube.com/watch?v=5aj6LAPCEF0